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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,916	07/09/2001	Michiaki Kohno	2001-0968A	2923

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	4

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,916	KOHNO ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claim 8 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combination of dolastatin 10 or vincristine as a tubulin polymerization inhibitor and PD98059 as a MAP kinase inhibitor for treating tumor, a method of treating tumor in vitro using the combination, and a pharmaceutical product comprising the combination; or, a method of enhancing the killing of cancer cells comprising administering a combination of p42/44 MAP kinase cascade inhibitor and vincristine, does not reasonably provide enablement for a combination of a microtubule-interfering agent and an ERK-MAP kinase inhibitor for treating tumor, where the microtubule-interfering agent and the ERK-MAP kinase inhibitor are

not defined; a method of treating tumor using the combination, or a pharmaceutical product comprising the combination. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-9 encompass a combination of a microtubule-interfering agent and an ERK-MAP kinase inhibitor for treating tumor (claims 1-6); a method of treating tumor using the combination (claims 7 and 8), and a pharmaceutical product comprising the combination (claim 9). The specification, however, only discloses cursory conclusions without data supporting the findings, which state that when a microtubule-interfering agent having an antitumor effect is used in combination with an ERK-MAP kinase cascade inhibitor, the antitumor activity of microtubule-interfering agent is remarkably potentiated (page 3, lines 23-28). There are no indicia that the present application enables the full scope in view of the use of a combination of a microtubule-interfering agent and an ERK-MAP kinase inhibitor for treating tumor as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the identities of the microtubule-interfering agent and the ERK-MAP kinase inhibitors used in the combination, and the in vivo treating conditions using the combination, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with variants except for the use of a combination of TZT-1027 or vincristine with PD98059 in treating tumor cells in vitro (Example, pages 9-13).

(3). The state of the prior art and relative skill of those in the art:

The prior art (Dent *et al.*, U.S. Patent 6,147,107) indicates the use of a p42/44 MAP kinase cascade inhibitor, PD98059 in combination with vincristine in treating tumor cells, where the administration of the inhibitor will potentiate the ability of chemotherapy of the antitumor agent. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of various microtubule-interfering agents and ERK-MAP kinase inhibitor used in the combination, and the in vivo treating conditions using the combination to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass the use of a combination of a microtubule-interfering agent and an ERK-MAP kinase inhibitor for treating tumor. However, the identities of various microtubule-interfering agents and ERK-MAP kinase inhibitor used in the combination, and the in vivo treating conditions using the combination are not sufficiently described in the specification, thus, the effect of the treatment is highly unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to the use of a combination of a microtubule-interfering agent and an ERK-MAP kinase inhibitor for treating tumor. The specification has indicated the use of a combination of TZT-1027 or vincristine with PD98059 in treating tumor cells in vitro, where PD98059 potentiates the antitumor activity TZT-1027 or vincristine (Example, pages 9-13), and general dosage for a microtubule-interfering agent and an ERK-MAP kinase inhibitor in the treatment (page 9, lines 10-19). However, the specification fails to demonstrate the use of various microtubule-interfering agents and ERK-MAP kinase inhibitors in the combination treatment of tumor in vivo. For example, the specification has not shown the treating conditions such as dosage, the time for in vivo treatment using a specific microtubule-interfering agent and a specific ERK-MAP kinase inhibitor in the combination treatment, nor has demonstrated the effect of the treatment. Furthermore, the specification has not shown how to extrapolate the in vitro results to in vivo effect. There are no working examples indicating the claimed methods using the combination. Since the specification fails to provide sufficient guidance on the identities of various microtubule-interfering agents and ERK-MAP kinase inhibitors used in the combination and the in vivo treating conditions, it is necessary to have additional guidance and to carry out further experimentation to assess the potentiating effect of the ERK-MAP kinase inhibitor in the combination therapy.

(6). Nature of the Invention

The scope of the claims includes the use of a combination of a microtubule-interfering agent and an ERK-MAP kinase inhibitor for treating tumor, but the specification does not show

the identities of various microtubule-interfering agents and ERK-MAP kinase inhibitors used in the combination, and the in vivo treating conditions sung the combination. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the treatment using various microtubule-interfering agents and ERK-MAP kinase inhibitors in the combination treatment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 1-9 are indefinite because of the use of the term "ERK-MAP". The term "ERK-MAP" renders the claim indefinite, it is unclear what the term indicates. The full spelled out words should be indicated at the first occurrence. Claims 2-4 are included in this rejection as dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

5. Claim 7 is indefinite because the claim lacks essential steps in the method of treatment of a tumor. The omitted steps are the effective amounts of a microtubule-interfering agent and an ERK-MAP kinase cascade inhibitor administered and the outcome of the treatment.

6. Claim 8 provides for the use of an ERK-MAP inhibitor, but does not set forth any steps involved in the method/process. It is unclear what method/process steps are or are not included in the claim. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

7. Claim 9 is indefinite because of the use of the term "and/or". The term "and/or" renders the claim indefinite, it is unclear whether the limitation after "and/or" is included or not, and if included is to be read as an alternative "or" or the conjunctive "and".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Dent *et al.* (U.S. Patent 6,147,107, filed on December 20, 1998).

Dent *et al.* teach a method of killing cancer cells comprising administering a p42/44 MAP kinase cascade inhibitor such as PD98059 in combination with a lethal agent such as

vincristine, and the MAP kinase inhibitor may be administered either in combination with or separately from the chemotherapeutic agent (column 4, lines 7-33; column 7, line 62-column 8, line 9; claims 1, 3, 4, 5, 7 and 9). The administration of such inhibitor will potentiate the ability of chemotherapy of the lethal agents to cause apoptosis of cancer cells, thus decreasing cancer recurrences (column 4, lines 34-37; claims 6 and 8). The p42/44 MAP kinase cascade inhibitor, PD98059 is an ERK-MAP kinase cascade inhibitor, and vincristine is a microtubule-interfering agent and a tubulin polymerization inhibitor (claim 2) because of the inherent property of the compound. Furthermore, vincristine has been cited as a tubulin polymerization inhibitor (page 5, lines 5-7) and PD98059 as an ERK-MAP kinase cascade inhibitor (page 7, lines 3-5) in the specification. Where Dent *et al.* disclose the combination of a microtubule-interfering agent and ERK-MAP kinase cascade inhibitor PD98059, it is administered as a composition which is a pharmaceutical (see e.g., column 8, line 42+ to column 9, line 21). Insofar as claim 9 recites packaging/instructions regarding use of the compounds in combination, the patent at columns 7 to 8 discuss the combined use. Thus, the teachings in the patent anticipate the pharmaceutical product in claim 9.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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March 7, 2003

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